UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/980,475 | 12/03/2001 | Akinori Arimura | 0032-0264P | 3377 |

2292 7590 07/09/2003

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

| EXAMINER | |
|---|---|
| RAO, DEEPAK R | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1624 | 6 |

DATE MAILED: 07/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/980,475 | Arimura et al. |
| **Examiner** | **Art Unit** |
| Deepak Rao | 1624 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Apr 29, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) *5 and 13* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 6-12, and 14-23* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Claims 1-23 are pending in this application.

### *Election/Restriction*

Applicant's election with traverse of Group I, claims 1-4 (in part), 6-12 (in part) and 14-23 (in part) in Paper No. 5 is acknowledged. The traversal is on the ground(s) that improper. This is not found persuasive because the instant claims do encompass separate and distinct inventions that have acquired separate status in the art, will support separate patents, and will require different fields of search for the respective inventions. Further, the instant application is a national stage application and therefore, must comply with the PCT Rule 13 according to which "A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature", see MPEP § 1893.03(d). Also, the instant claims do not meet the 'unity of invention' requirements as defined in Administrative Instructions under the PCT. The relevant information from MPEP is provided below for convenience.

ANNEX B
UNITY OF INVENTION
PART 1
INSTRUCTIONS CONCERNING UNITY OF INVENTION

**Markush Practice.** The situation involving the so-called Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2 . In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2 , shall be considered to be met when the alternatives are of a similar nature.

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B) (1) a common structure is present, i.e., **a significant structural element is shared by all of the alternatives**, or
(B) (2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.
(ii) In paragraph (f)(i)(B)(1), above, the words significant structural element is shared by all of the alternatives refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together.
(iii) In paragraph (f)(i)(B)(2), above, the words recognized class of chemical compounds mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.
(iv) The fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention.
(v) When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity shall be raised.

As can be seen from above, Unity of invention is deemed to be present if both conditions (A) and (B) are met. A review of the structural Formula (I) shows that there is no 'significant structural element' common to all alternatives, i.e., rings A, B and C can independently be aromatic carbocyclic or heterocyclic rings that are separated by spacer groups $V^1$ and $V^2$ and further, ring A is substituted by -X-Y. Since there are numerous variations among the members of Formula (I), each separate combination of the members establishes a different "significant structural element" upon which a reasonable search and examination may take place. Further, these alternatives do not belong to a recognized class of compounds. Therefore, the instantly claimed generic structure does **not** meet the criteria of (B)(1) and thus, lacks unity with any of the other combinations. The generic structure does **not** satisfy the criteria of (B)(2) because all of the alternatives do not belong to a recognized class of chemical compounds in the art.

The requirement is still deemed proper and is therefore made FINAL.

Claims 5 and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Applicant's election of the species of Compound No. I-6 (page 26, Table 2) is acknowledged. Applicant submits that claims 1-4, 6 and 8-23 read on the elected species. As the elected species was found in the prior art, the Markush-type claims were examined to the extent of the searched subgenus around the elected species, i.e., ring C is pyridinyl; rings A and B are phenyl. The generic subject matter drawn to the non elected species from claims 1-4, 6-12 and 14-23 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

### *Claim Objections*

Claim 18 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can not depend from any other multiple dependent claim. See MPEP § 608.01(n).

### *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a therapeutic agent for the treatment of rheumatoid arthritis, does not reasonably provide enablement as **prophylactic agent** for the treatment or **prevention** of all other diseases encompassed by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The instant claims are drawn to "pharmaceutical composition for use as a Th2 differentiation inhibitor which is a therapeutic or **prophylactic** agent against autoimmune disease" or "a method for treating and/or **preventing** a disease caused by Th2 cells...." and the specification provides allergic diseases and autoimmune diseases as the diseases associated with Th2 inhibiting activity, see page 1. First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is as Th2 differentiation inhibitors, useful to treat diseases, which include allergic diseases, autoimmune diseases, etc. Test assays, procedures and inhibitory data for a few of the exemplified compounds are provided in the specification in pages

72-78, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. Further, all the compounds actually tested are structurally very different from the other compounds of the claims such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the instantly claimed compounds. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, the instant claims recite 'treating or **preventing** a disease caused by Th2 cells...', and there is no disclosure regarding how all these assorted types diseases are treated or **prevented**. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat any disease embraced by the claims.

There is no common mechanism by which all allergic diseases arise. See the uncertainty expressed in a state of the art reference, Woodfolk et al., (PubMed Abstract enclosed) "the question why some individuals develop allergic disease and others do not remains largely unanswered". Accordingly, therapeutic or **prophylactic** treatment for these diseases are

normally tailored to the particular type of allergy or infection present and there is no "magic bullet" against all diseases encompassed by the instant claims. Regarding the T helper cell responses, Ji et al. (PubMed Abstract enclosed) disclose that "the role of Th subsets in the disease and the molecular basis of pathogenesis are unclear". Also, see Jaffar et al. (PubMed Abstract enclosed) "The cellular events that serve to regulate lung mucosal Th2 responses and limit allergic inflammatory reactions are unclear". Further, Elias (Am. J. Respir. Crit. Care Med.) express that "At present, the matrix alterations induced by Th2 cytokines, their mechanism(s) of generations and degree of reversibility, and the role of chronic Th2 cytokine production in the pathogenesis of airway remodeling are poorly understood", see page S170.

The instant claims recite the use of the compounds as '**prophylactic agent**' or 'a method of treating or **preventing**' the above diseases. Therefore, the scope of the claims includes not only treatment but also "**prevention** of a disease" which is not adequately enabled solely based on the kinase inhibitory activity of the compounds provided in the specification. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21,

1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6, 7, 19, 20, 21, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim 4 recites the limitation "wherein both of $V^1$ and $V^2$ are single bonds" in line 2. There is insufficient antecedent basis for this limitation in claim 1 on which claim 4 is dependent. Claim 1 recites that "one of $V^1$ is a single bond and the other is -O-, ..." and does not specify that both $V^1$ and $V^2$ can be single bonds.
2. Claim 6 contains Formula (Ib) and recites the limitation that "ring C is an optionally substituted 5- or 6-membered heterocyclic ring", see lines 3-4. There is insufficient antecedent basis for this limitation in claim 5 on which claim 6 is dependent. Claim 5 discloses Formula (Ia) wherein all three rings are 'phenyl' rings.
3. Claim 7 contains Formula (Ic) and recites that 'each of rings A, B and C are independently benzene or 5- or 6-membered heterocyclic ring', see lines 3-8. There is insufficient antecedent basis for this limitation in claim 5 on which claim 7 is dependent. Claim 5 discloses Formula (Ia) wherein all three rings are 'phenyl' rings.
4. Claim 19 recites the limitation "the compound represented by Formula (I) according to claim 1", see lines 2-3. There is insufficient antecedent basis in claim 1 on which claim 19 is dependent. Claim 1 is drawn to a pharmaceutical composition comprising a compound of Formula (I). Claim 20 also contains the same discrepancy.

5. Claims 21 and 22 provide for the use of the compounds of Formula (I), but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

6. Claim 23 contains Formula (Ib) and recites the limitation that "ring C is an optionally substituted 6-membered heterocyclic ring", see lines 3-4. There is insufficient antecedent basis for this limitation in claim 5 on which claim 6 is dependent. Claim 5 discloses Formula (Ia) wherein all three rings are 'phenyl' rings.

***Claim Rejections - 35 U.S.C. § 101***

Claims 21 and 22 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-4, 6-12 and 14-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanimoto et al., WO 99/38829 (published August 5, 1999). The instantly claimed pharmaceutical composition comprising a compound of formula (I) reads on the reference disclosed composition. See the structural formula I in page 2 and the species of Example 5 (page 176). The composition is disclosed to have immunosuppressant or anti-allergic activity and useful as a therapeutic agent for allergic diseases, etc. (See col. 96, lines 46-57 of English equivalent document, U.S. Patent No. 6,562,817 which is issued from an application resulting from the national stage entry of the instant WIPO document). The instant claims 19-20 read on the prior art taught therapeutic effect because the instant claims are drawn to administration of the prior art compounds, in same dosages, to the same population. The therapeutic effect of claims 19-20 is evident from the specification page 53. The prior art also teaches that the compounds are useful in the treatment of allergic diseases, etc. which fall within the scope of the instant claims and therefore, the instantly claimed mechanism of Th2 differentiation inhibition is inherently taught in the reference.

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-12 and 14-23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-12, 42-49 and 73-79 of U.S. Patent No. 6,562,817. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims substantially overlap the reference claimed invention. The reference claims are also drawn to a pharmaceutical composition comprising a compound that is structurally similar to the compound of the instantly claimed composition. One of ordinary skill in the art would have been motivated to select any of the

compounds taught in the reference because he would have had the reasonable expectation of obtaining similar pharmaceutical therapeutic utility.

***Duplicate Claims***

Applicant is advised that should claim 1 be found allowable, claims 17 and 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See.MPEP § 706.03(k). Claims 17 and 18 recite an intended use for the composition but do not further limit claim 1.

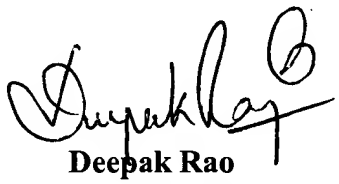
Receipt is acknowledged of the Information Disclosure Statement filed on December 3, 2001 and a copy is enclosed herewith.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.



**Deepak Rao**
**Primary Examiner**
**Art Unit 1624**

July 8, 2003